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Response to Public Comments for 1,2-Benzisothiazol-3(2H)-one (CAS #2634-33-5)

Summary:

Based on public comments, the Michigan Department of Environment, Great Lakes, and Energy (EGLE), Air Quality Division (AQD) has reviewed the basis for the Initial Threshold Screening Level (ITSL) for 1,2-benzisothiazol-3(2H)-one. As a result of that review, the AQD will rescind the established ITSL.

Background:

Revisions to the Air Pollution Control Rules[1] were promulgated December 22, 2016. Subsequently, the AQD published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 30 days: May 15, 2019 through June 17, 2019. The AQD is required to respond to these comments within 60 days; the latest date for response is August 16th.

[1] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II, Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994, PA 451, as amended (NREPA).

Comments and Responses:

Comment:

The commenter would like verification of the appropriateness of using the default screening level value in lieu of existing toxicity data for the toxic air contaminant (TAC). Rule 232 (1)(i) was specifically referenced in which it states, "if an initial threshold screening level cannot be determined under the provisions of subdivision (a), (b), (c), (d), (e), (f), (g), or (h) of this subrule, then the initial threshold screening level = 0.1 ug/m³."

Response:

The existing toxicity database for 1,2-benzisothiazol-3(2H)-one (which is also known as "BIT") is inadequate for ITSL derivation, because there is a lack of quantitative inhalation exposure studies on which to base the ITSL. There is a need for these inhalation studies, because the weight of the evidence suggests that critical effects for this TAC are related to portal-of-entry irritancy and respiratory sensitization (see Table 1). Chemicals that are categorized as sensitizers have been shown to cause portal-of-entry effects, strong irritation, and decreased lung function. Therefore, routes of exposure other than inhalation are inappropriate for route-to-route extrapolation and derivation of inhalation health protective benchmarks. Although a potential ITSL based on an oral study is described in the TAC justification, that potential ITSL was drafted for comparison to the level of health protection achieved under the default value. Given the limitations for appropriately extrapolating across routes of exposure, the potential ITSL based on the oral study will not be used for the final ITSL.

Table 1. BIT Toxicity Studies that Indicate Portal-of-Entry Critical Effects

Study Type (Reference)	Critical Effect	Why Inappropriate for ITSL Development *
Human case studies following inhalation exposure (HSDB, 2015; Moscato et al., 1997; TSCA, 2018)	Respiratory sensitization and respiratory irritation	The exposure concentrations needed to determine dose-response relationships are not known. Sample sizes are too small and case studies do not characterize well-controlled and designed studies.
In vivo eye irritation study (ECHA, 2018)	Eye irritation	Eye irritation indicates portal-of-entry effects, so route-to-route extrapolation is not appropriate.
In vivo dermal study (EPA, ChemView)	Dermal irritation	Dermal irritation indicates portal-of-entry effects, so route-to-route extrapolation is not appropriate.
Controlled human dermal study (Madsen and Andersen, 2016)	Contact dermatitis/Allergic sensitization	Allergic sensitization indicates critical effects may manifest in the respiratory system, so route-to-route extrapolation is not appropriate.

*EPA, 1994, provides guidance for derivation of inhalation reference concentrations. Chapters 2 and 4 outline minimal requirements needed for use of human data as well as route-to-route extrapolation. Likewise, Gerrity and Henry, 1990 provide guidance for use of route-to-route extrapolation.

The approach of using the default ITSL has been done historically within the AQD in similar situations, where existing chemical-specific data was deemed inappropriate for ITSL derivation based on the weight of the evidence indicating portal of entry effects and the absence of adequate inhalation data. Examples include the structurally and toxicologically similar chemical 2-methyl-4-isothiazolin-3-one (CAS #2682-20-4) where evidence of skin sensitivity was noted in the toxicological review (MDEQ, 1999).

However, with further review into the basis for the default ITSL, it was determined that the default ITSL was not specifically designed to be protective for health effects from sensitizers or portal of entry irritants (DNR, 1981; MDEQ, 1997). The original default value was derived with consideration for substances with LD50 values less than or equal to 5 mg/kg. Substances with these LD50 values were classified as “super toxic” (DNR, 1981). The most current default value is based on the 5^{th} and 10^{th} percentile of ITSLs available at the time of re-evaluation. Within both the original default value and the most current default value considerations, sensitizers and portal of entry irritants, in particular, may not be accounted for.

For LD50 testing, strong irritant effects are among initial considerations for not administering the test (OECD, 2001). Thus, LD50 testing may not capture TACs of concern when irritancy is a critical effect. Similarly, the derivation method used for the most current default value suggests that it may not be health protective for these critical effects. The complete list of TACs used to derive the default ITSL in 1997 is not known. However, the chemicals of “high concern” list, which subsequently became Table 20 in the Air Toxics Rules and would encompass TACs in the 5th percentile range, was generated around the same time. This list of high concern TACs includes TACs with sensitization and/or potent irritancy as the critical effect. Taken together, these factors indicate that the default ITSL may not be health protective for BIT. As a result, the default ITSL is being rescinded at this time and BIT will be evaluated on a case by case basis.

Summary and Conclusions:

While there is exposure toxicity data for BIT that indicate sensitization and portal-of-entry effects in occupational (and consumer) exposure scenario(s), the available data is not adequate to derive a screening level. When a well-designed dose-response study using an appropriate route of exposure is not available, Rule 232(1)(i) is typically used for ITSL derivation. However, the default ITSL, 0.1 µg/m^3, annual averaging time, may not be health-protective for acute effects of sensitizers. As a result, the default ITSL will not be applied to BIT, and the ITSL is being rescinded.

The primary AQD reviewer for these comments was Keisha Williams, Senior Toxicologist, AQD Toxics Unit. The secondary reviewer was Mike Depa, Senior Toxicologist, AQD Toxics Unit.

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